EXHIBIT F

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Illana Gozes et al. Application No.: 10/748,765 Filed: December 29, 2003 For: METHODS OF TREATING AND/OR PREVENTING AUTOIMMUNE DISEASES Customer No.: 20350	Confirmation No. 8714 Examiner: C. M. Woodward Technology Center/Art Unit: 1647 DECLARATION OF DR. ILLANA GOZES UNDER 37 C.F.R. §1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Illana Gozes, Ph.D., being duly warned that willful false statements and the like are punishable by fine or imprisonment or both (18 U.S.C. § 1001), and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true, and statements made on information or belief are believed to be true and correct.

2. I am currently a Professor of clinical biochemistry at Tel Aviv University I am Director of the Adams Super Center for Brain Studies & Edersheim Levi-Gitter fMRI Institute, also at Tel Aviv University. I have been the incumbent of the Lily and Avraham Gildor Chair for the Investigation of Growth Factors at Tel Aviv University, since 1997. I am also the Chief Scientific Office and Director at Allon Therapeutics, Inc. in Vancouver, Canada. I received a Ph.D. from The Weizmann Institute of Science in 1979, and was a Haim Weizmann Postdoctoral Fellow at the Massachusetts Institute of Technology from 1979-1980. I was a Research Associate and Visiting Scientist at the Salk Institute and the Scripps Clinic and

Research Foundation from 1981-1982. I was a Senior Scientist/Associate Professor at The Weizmann Institute of Science from 1982-1989. I was a visiting scientist in developmental neurobiology at NICHD, NIH from 1989-1990. My affiliation with Tel Aviv University began in 1990. I was a Fogarty-Scholar-in-Residence at NIH from 1995-1996 and an adjunct scientist in developmental neurobiology at NIH from 2003-2004.

3. I have received a number of scientific awards and prizes, including the Juludan Prize and the Teva Founders Prize for exceptional scientific studies and the Bergmann Prize and the Neufeld award for outstanding/leading US-Israel BSF grant proposals. I am currently Editor-in-Chief of The Journal of Molecular Neuroscience and I currently sit on the editorial boards of the American Journal of Alzheimer's Disease, the International Journal of Peptide Research & Therapy and the journal Peptides. I am an author on more than 197 research papers and am an author or co-author of numerous reviews and book chapters. A copy of my curriculum vitae is attached hereto as Exhibit G and includes a list of selected publications.

4. The present invention is a method of treating multiple sclerosis (MS) by administering a therapeutically effective amount of an ADNF III peptide to a patient. The treatment includes administration of a peptide that comprises the core active site sequence of ADNF III, *i.e.*, the amino acid sequence NAPVSIPQ known as "NAP." NAP is the smallest peptide that exhibits the same activity as full-length ADNF III. Use of D-amino acid NAP and ADNF III peptides for treatment of MS are also claimed.

5. I have read and am familiar with the contents of this patent application. In addition, I have read an Office Action, dated April 29, 2008, received in the present case, as well as the cited references. It is my understanding that the Examiner alleges that the claimed invention is obvious in view of Gozes *et al.*, US patent No. 6, 613,740, WO98/35042 and Brenneman *et al.*, US 2002/0111301; or Brenneman *et al.*, Gozes *et al.*, US Patent 4,587,046 and Voet *et al.*, Biochemistry 2nd Ed., page 67. Specifically, the Examiner states that one of skill would have predicted that ADNF III polypeptides could be used to treat MS because the cited references disclose the ADNF III polypeptides can be used to treat the neuro-auto immune disorder Guillian-Barre syndrome. The Examiner also states that one of skill would have a

reasonable expectation of success because ADNF peptides treat conditions related to neuronal cell death.

6. This declaration is provided to demonstrate that the cited references do not provide motivation for their combination to arrive at the claimed methods and do not predict that the claimed methods would result from their combination. Moreover, the invention is based on a surprising result: ADNF III peptides inhibit the proliferation of immune cell and decrease the levels of cytokines secreted by immune cells.

7. Before the filing date of the priority application, ADNF III was known to prevent neuronal cell death. The ability of ADNF III to inhibit neuronal cell death was first demonstrated in vitro using isolated neuronal cells. *See, e.g.*, US Patent No. 6,613,740, Gozes *et al.*, Figs. 6A-C, 7A-B and column 58, line 23 through column 59, line 4. Thus, other cell types, *e.g.*, immune cells, are not required for inhibition of neuronal cell death by ADNF III.

8. Before the publication of the present application, it was not known that ADNF III affects non-neuronal cells, including immune cells. It was not known that ADNF III inhibits of proliferation of immune cells. It was not known that ADNF III decreases the amount of cytokines, *e.g.*, of tumor necrosis factor-α (TNF-α) and interleukin-12 (IL-12) secreted by immune cells. These new activities of ADNF III are disclosed in the specification and are also confirmed in post-filing data.

9. The specification provides evidence that ADNF III peptides inhibit proliferation of immune cells using an art accepted animal model of MS, myelin-oligodedrocyte glycoprotein (MOG)-induced chronic experimental autoimmune encephalomyelitis (EAE) in mice.

10. The specification demonstrates the effect of ADNF III peptides on the MOG-induced chronic EAE model at paragraphs [103]-[106]. EAE was induced by immunization of mice with the peptide encompassing amino acids 35-55 of rat MOG. Peptide synthesis was carried out by the Weizmann Institute Synthesis Unit using a solid-phase

technique, on a peptide synthesizer (Applied Biosystems Inc., Foster City, CA City). Six weeks old C57/b mice (Tel-Aviv University) were injected (subcutaneous) in the flank with a 200μl emulsion containing 300μg MOG peptide in complete Freund adjuvant (CFA) and 500μg Mycobacterium tuberculosis (Sigma Israel). An identical booster immunization was given on the other flank one week later. Ten days following the encephalitogenic challenge, the MOG-treated mice were observed daily and the clinical manifestations of EAE were measured by the following score: 0 = no clinical symptoms; 1 = loss of tail tonicity; 2 = partial hind limb paralysis; 3 = complete hind limb paralysis; 4 = partial frontal limb paralysis; 5 = complete frontal limb paralysis; 6 = death.

11. For treatment, mice were administered with NAP (intranasal) 0.1 microgram/mouse in a mixture containing 7.5 mg/ml sodium chloride, 1.7 mg/ml citric acid monohydrate, 3.0 mg/ml disodium phosphate dehydrate and 0.2 mg/ml of a 50% benzalkonium chloride solution. The nasal administration was given daily, 1 hour after MOG injection and was continued and given once a day, 1 hour prior to testing. Control animals received the above mixture without NAP. In the example here, NAP's daily treatment began 10-14 days prior to the MOG injection. Results showed that NAP significantly improved the clinical outcome of the animals, day 11 on, $P<0.01$, t-test (Figure 1 of the specification).

12. An additional experiment determined proliferative T-cell response. Results indicated that NAP inhibited the immune response (cell proliferation, Fig. 2 of the specification) *in vivo* as the proliferative response of splenocytes was much reduced ($P<0.01$) in the mice treated with NAP as compared to untreated mice. Furthermore, addition of MOG resulted in increased proliferation in the splenocytes of untreated animals, even at 2 micrograms/well of MOG, $P<0.05$). In contrast, even at 25 micrograms MOG, the proliferative response NAP treated animals did not increase.

13. Post-filing results confirm the ability of ADNF III peptides to decrease levels of tumor necrosis factor-α (TNF-α) and interleukin-12 (IL-12) and also confirm the anti-proliferative effect of ADNF III peptides on T-cells that are activated by a MOG antigen.

14. Quintana *et al.*, *Ann. N.Y. Acad. Sci.* 1070:500-506 (2006) is submitted as Exhibit H. RAW 264.7 cells, a transformed macrophage cell line, were activated by LPS in the presence or absence of an ADNF III peptide. Results are shown at page 503 and Figure 2. As levels of ADNF III peptide were increased, levels of TNF-α and IL-12 secreted by the RAW 264.7 cells decreased. Thus, Quintana *et al.* demonstrate that ADNF III peptides decrease levels of TNF-α and IL-12 secreted by immune cells. As these experiments were done using isolated immune cells, the demonstrate that the ADNF III effect on immune cells is independent of its effect on neuronal cell.

15. The references cited by the Office Action demonstrate that ADNF III peptides prevent neuronal cell death and are silent on an ADNF III function related to immune cells. In my opinion, the ability of ADNF III to prevent neuronal cell death did not suggest or predict that ADNF III would inhibit cell proliferation, including immune cell proliferation. Prevention of neuronal cell death by ADNF III did not suggest or predict that administration of ADNF III would independently decrease the levels of cytokines secreted by immune cells. Therefore, in my opinion, one of skill would consider the discovery that ADNF III peptide inhibits immune cell proliferation to be a surprising result.

16. In view of the forgoing, in my opinion, the cited references do not teach, suggest, or predict the claimed method to treat MS. In addition, the effect of ADNF III peptides on the immune response was a surprising result.

Date: ___September 25, 2008_____ By:____

Illana Gozes, Ph.D.

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